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4

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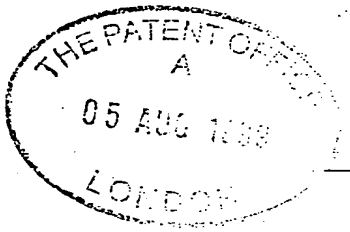

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The Patent Office

Request for grant of a Patent

Form 1/77

5 AUG 1999

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: Treatment of Cancers

❷ Applicant's details

❑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: Pharma Mar, S.A.

Country *(and State of incorporation, if appropriate)*: SPAIN

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases**, please give the following details:

Address: Calle de la Calera, 3
Poligono Industrial de Tres Cantos
28760 Tres Cantos, Madrid, Spain
SPAIN

UK postcode *(if applicable)*

Country

ADP number *(if known)*: 551729700 2

1, 2e and 2f: If there are further ... ants ... ase provide details on a separate sheet of paper.

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Yes [X] No [ ] ➡ ***go to 3b***

⬇ ***please give details below***

Agent's name: Marks & Clerk

Agent's address: 57-60 Lincoln's Inn Fields
LONDON
WC2A 3LS.

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Agent's ADP number: 18001

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3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

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230P81051

❺ Claiming an earli r application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ ***go to 6***

⬇

please give details below

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❑ filing date

(day month year)

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❻ Declaration of priority

❻ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

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4/4

❼ *The answer must be 'No' if: any applicant is not an invento[illegible] re is a [illegible]ventor who is not an applicant,* ***or*** *any applicant is a corporate body.*

❼ Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes ☐ No ☒ ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	—		
Claim(s)	—	Description	4 / 23
Abstract	—	Drawing(s)	—

8b Which of the following documents also accompanies the application?

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Priority documents *(please state how many)*	—
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Treatment of Cancers

The present invention relates to the treatment of cancers.

US Patent 5,089,273 relates to compounds identified as ecteinascidins. In particular, it relates to ecteinascidins 729, 743, 759A, 759B and 770. The compounds are disclosed to have antibacterial properties and some are also useful as antitumor agents.

We have now found that ecteinascidin 743 has exceptional activity in the treatment of sarcomas, mesotheliomas and cartilage tumours. A sarcoma is a cancer arising from connective tissue such as muscle or bone. A mesothelioma is a tumour of the mesothelium of the pleura, pericardium or peritoneum.

Thus, the present invention provides a method of treating any mammal, notably a human, affected by a sarcoma, mesothelioma or cartilage tumour which comprises administering to the affected individual a therapeutically effective amount of ecteinascidin 743, or a pharmaceutical composition thereof. Examples of human sarcomas to be treated include osteosarcomas and soft tissue sarcomas, leiomyosarcomas, fibrosarcomas and mesotheliomas.

The present invention also relates to pharmaceutical preparations, which contain as active ingredient ecteinascidin 743, as well as the processes for its preparation.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the composition of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous

administration. Intravenous delivery may be carried out over any suitable time period. We prefer that infusion times of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 2 to 4 weeks. An example of a 3 hour infusion treatment is given in the abstract by Twelves et al., at the end of this text.

Pharmaceutical compositions containing ecteinascidin 743 may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of ecteinascidin 743 of this invention will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);

b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);

c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosphamide);

d) drugs which target DNA such as the antracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;

e) drugs which target topoisomerases such as etoposide;

f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;

g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

h) alkylating drugs such as platinum drugs (cis-platin, carboplatin, oxaliplatin , paraplatin) or nitrosoureas;

i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;

j) gene therapy and antisense agents;

k) antibody therapeutics; and

l) other bioactive compounds of marine origin, notably the didemnins such as aplidine.

The present invention also extends to the compounds for use in a method of treatment, and to the use of the compounds in the preparation of a composition for treatment of cancer.

Example

A group of 22 sarcoma patients, including soft tissue sarcomas (fibrosarcomas, leyomiosarcomas, mesotheliomas, etc.) and bone sarcomas (osteosarcomas) have been treated at the maximum tolerated dose (MTD) and recommended dose (RD) during phase 1 trials. Patients' characteristics include 10 men and 12 women, median age 52 (17-68) years, all pre-treated with anthracyclines or alkylators with 1 to 4 previous chemotherapy treatments, median performance status (PS) 1 (0-1) (ECOG), median number of metastatic sites 2 (1 to 7) were treated with ET-743. 11 patients were treated at a dose of 1500 mcg/m2 or over during a 24 hour infusion (9 patients into a clinical trial and 2 patients as compassionate use). One patient was treated at 1500 mcg/m2 in the 3 hour infusion study; 3 patients in the daily times five study (1 hour infusion x 5 days) at doses over 1625 mcg/m2 and 7 patients in the 72 hour continuous infusion at doses over 1050 mcg/m2.

In this group of patients the following responses have been observed: six partial responses (2 osteosarcomas, 2 leiomyosarcomas, 1 fibrosarcoma, 1 mesothelioma) 3 of which lasting over 4 months, one minor response and 4 stabilisations (WHO criteria).

An example of the use of Et-743 against chondrosarcoma cells is given in the accompanying abstract by Hornicek *et al.* Other abstracts relate to a possible mechanism of action of Et-743.

A Phase I and Pharmacokinetic (PK) study of ET-743 evaluating a 3 hours (h) intravenous (iv) infusion (I) in patients (pts) with solid tumors.

C. Twelves[1], H. Hoeckman[3], A. Bowman[2], J.H. Beijnen[4] , M. Faber[5], C. Guzman[6], A. Anthoney[1], J. Smyth[2], J. Jimeno[6].
[1]ECSG/EORTC (Glasgow[1] and Edinburgh[2], UK; Amsterdam[3], NL), [5]NDDO (Amsterdam, NL) [4]Slotervaart Hospital, (Amsterdam, NL), [6]PharmaMar R&D (Tres Cantos, Spain).

ET-743 is a marine derived compound currently in phase II using an iv infusion (I) for 24 h q 3 weeks. In this dose finding study pts with advanced/resistant solid tumors received ET-743 as an iv 3 h I every 3 weeks. Thirty two pts (median age = 55 y., PS = 1, male/female 14/17) have been treated. The starting dose of 1000 mcg/m^2 is the recommended dose of ET-743 given as a 1 h I. The following dose levels have been assessed (pts/cycles): 1000 (3/8), 1300 (6/16), 1500 (6/17), 1800 (4/5) and 1650 (13/29) mcg/m^2. The maximal tolerated dose (MTD) is 1800 mcg/m^2 with grade (G) 4 thrombocytopenia and severe fatigue the dose limiting toxicities. The 1650 mcg/m^2 dose level was generally well tolerated with G3-4 neutropenia in 3/13 pts and thrombocytopenia in 2/13 patients; 1 pt had febrile neutropenia. Transient, non-cumulative rises in serum transaminases were observed in 9/13 pts at 1650 mcg/m^2. There were no toxic deaths.

Pharmacokinetic analysis (LC/MS/MS/ES) is ongoing; initial data confirm high clearance (median 38.34 L/h* m^2) and volume of distribution (1231 L/ m^2). AUCs achieved with the 1650 mcg/ m^2 3h I are similar to those using the 1500 mcg/ m^2-24 h I (median 43.20 and 43.32 h*ug/l, respectively). At the 1500 mcg/m^2 dose level, a pt with relapsed, metastatic leiomyosarcoma previously treated with chemotherapy and pelvic RT had a complete remission; (8+cycles, time to progression = 32+wks); a further 8 pts are ongoing at 1650 mcg/ m^2, with tumor assessment awaiting. Our results indicate that the 3 h I is an active, feasible out-patient schedule for ET-743. The proposed phase II dose for good risk pts is 1650 mcg/ m^2.

3 hour.

In vitro effect of the tetrahydroisoquinoline alkaloid - Ecteinascidin -743 (ET-743) on chondrosarcoma cells.

Hornicek, Francis J.; Weissbach, Lawrence; Nielsen, G. Petur; Fondren, Gertrude; Harmon, David; Jimeno, Jose; Chabner, Bruce A., Faircloth, Glynn T. Massachusetts General Hospital and PharmaMar, Inc.

Tumors of cartilage comprise the most common primary connective neoplasms of the skeleton. They have a variety of presentations and behave unpredictably. Treatment modalities have included radiation therapy (XRT) and chemotherapy but have yielded disappointing results except in patients with dedifferentiated and mesenchymal CHSAs. Currently, the most effective treatment for CHSA is surgical resection. As a first step in developing more effective treatments we have begun to propagate CHSA cell lines from explants and have characterized various properties of these cell lines.

We have performed RT-PCR analysis on cultured CHSA cells after isolating total RNA from monolayer cultures established from surgically resected specimens that have not been exposed to chemotherapy or XRT. Both type II and type IV collagen mRNA have been detected. The fact that the expression of the type II collagen gene, a classical marker for differentiation cartilage is found in these cultured cells suggests the retention of a chondrocytic character.

Ecteinascidin-743 (ET-743), a tetrahydroisoquinoline alkaloid isolated from the marine ascidian Ecteinascidia turbinata, is highly cytotoxic to various tumor cells, but bone and cartilage tumor cells have not been tested for their sensitivity to this compound. Due to the lack of effective treatments currently available for CHSA, we tested the effect of ET-743 on cultured CHSA cells. At a concentration of 1 nM, ET-743 was cytotoxic for these cells, and flow cytometry of the treated samples indicated an inhibition of progression through the cell cycle. There was a dose dependent toxicity in the range of 1 to 100 nM, and $S+G_2+M$ phase cells decreased correspondingly. These results support earlier data on the cellular toxicity of ET-743 for cancer cells.

Except for surgery none of the conventional treatment modalities are successful in managing patients with CHSA. The reasons for this poor response to chemotherapy and XRT remain unknown. New approaches are therefore warranted in the treatment of CHSA. The demonstration that ET-743 inhibits proliferation of these cells lends itself to further investigation as a new avenue of treatment for CHSA.

Mode of action of Ecteinascidin 743 (ET-743).

D'Incalci Maurizio; Istituto Mario Negri, Milan, Italy.

ET-743 is a tetrahydroisoquinoline isolated from *Ecteinascidia Turbinatata* with striking pre-clinical antitumor activity which is undergoing phase II trials. ET-743 appears to recognize DNA through a direct read out mechanism involving specific hydrogen bound donor-acceptor pairs between a subunit of the drug and the minor groove. The minor groove alkylation at N2 position of guanine (Pommier et al., Biochem. 35:13303, '96, Moore et al., JACS, 119:5475, '97) bends DNA into the major groove (Hurley, personal comm.), thus causing a perturbation of DNA structure that is unique. ET-743, at concentrations pharmacologically reasonable, does not cause DNA breaks or DNA protein cross links, suggesting that it is not a topoisomerase I poison. S. Cerevisiae with topo gene I deletion showed the same sensitivity to ET-743 as control yeast, demonstrating that topoisomerase I is not the relevant target. The deletion of Rad 51 gene confers high sensitivity to ET-743, indicating that DNA repair is crucial for the drug action. In cell lines deficient in Nucleotide Excision Repair (NER) a paradox effect was observed. NER deficient cells which were hypersensitive to conventional alkylating drugs or cisplatin were 6-8 fold less sensitive to ET-743. Cells which were deficient in DNA-dependent PK or in AT were instead more sensitive to ET-743 than control repair proficient cells. Mismatch repair deficiency did not modify the sensitivity to ET-743. Although the precise mode of action of ET-743 is not elucidated yet, the data obtained so far indicate that it has a unique mechanism of interaction with DNA and DNA binding proteins.

Interference of transcriptional activation by the anti-neoplastic drug ET-743.

Minuzzo Mario and Mantovani Roberto; Dip. Genetica e Biologia dei Microrganismi, Università degli Studi di Milano, Milan, Italy.
Faircloth Glynn T.; PharmaMar USA, Inc., Cambridge, MA, USA.
D'Incalci Maurizio, Istituto Mario Negri, Milan, Italy.

Et743 is an alkaloid isolated from the tunicate Ecteinascidia turbinata,
currently under phase II clinical trials for its potent anti-cancer activity, that was shown to bind DNA in the minor groove and form covalent adducts with some sequence-specificity. We show that Et 743 selectively inhibits in vitro CCAAT-box binding of NF-Y, a trimeric transcription factor, targeting the regulatory NF-YA subunit. We assayed Et743 function in vivo by deriving stable NIH3T3 lines with integrated HSP70 promoter, which is dependent on NF-Y and on the Heat Shock Factor (HSF). Upon heat induction, the drug blocks transcription rapidly, at pharmacological concentrations -2/30nN- and in a CCAAT-dependent way. The Distamycin-like alkylating compound Tallimustine has no effect, even in the microM range.
The activity of the CCAAT-less SV40 promoter is not affected, indicating that Et743 is not a general Pol II inhibitor. Extracts of drug-treated cells showed normal NF-Y and increased HSF binding, suggesting that inhibition of activator(s) binding is not responsible for lack of promoter activity. We hyopothesize that this new marine compound is a promoter specific transcriptional interfering agent.

Changes in gene expression in tumor cells exposed to the two marine compounds Aplidine or ET-743 and Aplidine by using cDNA microarrays.

Broggini Massimo, Marchini Sergio and D'Incalci Maurizio; Istituto Mario Negri, Milan, Italy.
Faircloth Glynn T. and Jimeno José; Pharma Mar, Cambridge, USA and Tres Cantos, Spain.

The present study was undertaken to investigate whether and at which extent two natural products such as ET-743 and Aplidine with a still poorly understood mode of action could induce early changes in the expression of genes encoding for proteins with crucial role in signal transduction, proliferation, cell cycle and apoptosis.
Igrov-1 cells were exposed to ET-743 active concentrations and total RNA was isolated after 0, 6 and 24 hours of treatment. For Aplidine, total RNA was isolated from MOLT-4 cells at 0, 1, 6 and 24 hours after treatment.
1 μg of total RNA was retrotranscribed in the presence of 32p-ATP using a mixture of specific primers (Clontech) and MMLV reverse transcriptase. Equal amounts of 32-P labeled RNA were hybridized to cDNA expression arrays (Clontech, human cancer) containing 588 human cDNAs. Hybridization and washing of the filters were performed according to manufacturer's instructions. Analysis was carried out using the ATLAS IMAGE 1.0 software (Clontech).
Initial analysis of the results in revealed changes the expression of genes playing important roles including for ET-743 p21/WAF, GADD45 and killer/DR5 and for Aplidine c-fms, ETR-1, FLT-1 topoisomerase II α, DNA-PK and ATM.
Studies are in progress to verify the observed changes of expression with other methods and to evaluate the relevance of these findings for the antitumor activity of these drugs.

Potent antitumor activity of ET-743 against human soft tissue sarcoma cell lines.

Li Weiwei, Jhanwar Suresh, Elisseyeff Yaroslav, and Bertino Joseph, R. Memorial Sloan-Kettering Cancer Center, New York, NY 10021

We examined the antitumor activity of ET-743, a novel marine natural product, in human soft tissue sarcoma (STS) cell lines. Nine cells lines (4 previously described in Int. J. Cancer 68:514, 1996, 4 new cell lines and HT-1080 a fibrosarcoma cell line) were exposed to ET-743 at different concentrations for 72 h and IC50 values of ET-743 for these cell lines were determined using a SRB cytotoxicity assay. Results showed that IC50's are particularly low for HT-1080 and for malignant fibrous histiocytoma (MFH) cell lines, HS-90, M-8805, M-9110 and M-9005 (<0.1 pM). IC50's determined in four other HSTS cell lines, HS-16 (mesenchymal chondrosarcoma), HS-18 (liposarcoma), HS30 (malignant hemangiopericytoma) and HS-42 (malignant mesenchymoma) ranged from 4 pM to 100 pM. Antitumor activity of ET-743 is also observed to be time-dependent and p53-independent in these STS cell lines. In contrast, ET-743 was less potent against other types of tumor; higher IC50's were observed in colon cancer cell lines such as HCT-8 (10 nM), HT-29 (3 nM) and HCT-116 (3 nM) and a breast cancer cell line, MCF-7 (20 nM). We conclude that ET-743 is highly active against STS cells, especially against MFH cells, and encourage trials of this drug in patients with STS.

Importance of DNA repair mechanisms for the sensitivity to ET-743.

Damia Giovanna, Silvestri Simonetta, Filiberti Laura, Broggini Massimo and D'Incalci Maurizio; Istituto Mario Negri, Milan, Italy.
Faircloth Glynn T.; Pharma Mar USA, Inc., Cambridge, MA, USA.

ET-743 is a tetrahydroisoquinoline alkaloid extracted from the tunicate *Ecteinascidia turbinata* with striking antitumor efficacy in pre-clinical systems and promising activity in the initial clinical investigations.
It binds DNA in the minor groove alkylating N2 position of guanine. In order to better define the mechanisms of ET-743 interaction with DNA, its sensitivity was evaluated in different cellular systems characterized by defined deficiencies in DNA repair pathways. Defects in mismatch repair pathway, that are usually associated with an increased resistance to methylating agents and cisplatinum, did not affect the cytotoxic activity of ET-743. On the contrary ET-743 displayed an unusual pattern of sensitivity in UV-sensitive NER (nucleotide excision repair) deficient mutant CHO cell lines, being eight and six fold more resistant in ERCC1 (excision repair cross-complementing) and in XPB (xeroderma pigmentosum) deficient cell lines respectively. DNA-double-strand break (DSB) repair pathway was also investigated using human glioblastoma cell lines MO59K and MO59J, respectively proficient and deficient in DNA-dependent protein kinase (DNA-PK). ET-743 was found to be more sensitive, with a two fold decrease in IC50 in cells lacking DNA-PK. An increase in ET-743 sensitivity was also observed in AT (Ataxia teleangectasia mutated) cells.
Although the molecular mechanisms underlying these effects have not been elucidated yet, the data strongly suggest that ET-743 has a unique mechanism of interaction with DNA.